September 26, 2019

Submitte[HYPERLINK "mailto:tox@tceq.texas.gov" \h]

Dr. Michael Honeycutt, Director
Toxicology, Risk Assessment, and Research Division
Texas Commission on Environmental Quality
[SHAPE * MERGEFORMAT]

Re: TCEQ Proposed Development Support Documents (DSDs) for Ethylene Oxide (EtO) Carcinogenic Dose-Response Assessment

Dear Dr. Honeycutt:

The Ethylene Oxide Panel (Panel) of the American Chemistry Council (ACC), submits its comments on the proposed TCEQ Development Support Document (DSD) for Ethylene Oxide (EtO) Carcinogenic Dose-Response Assessment (TCEQ, 2019[1]). The Panel supports the inhalation-based unit risk factor (URF) derived by TCEQ for EtO. TCEQ's approach to ground-truth the selection of the extrapolation model based on biological and epidemiological evidence is a critical missing step in EPA's IRIS EtO assessment (IRIS, 2016[2]). An overly conservative assessment can result in misplaced public concern, supply chain disruption of critical products, and the unnecessary use of resources.

The TCEQ proposed EtO DSD calculated a URF of 2.5E-6 per ppb (1.4E-6 per $\mu g/m^3$) and a 1/100,000 extra risk chronic health-based effects screening level for non-threshold dose response cancer effect of 4 ppb (7 $\mu g/m^3$) based on the NIOSH epidemiology study and an assumption of a 15-year exposure lag period. Although ACC has previously recommended a different approach based on the two strongest epidemiology studies and zero lag period[3,4], ACC finds the TCEQ proposal acceptable because it is much more scientifically sound, biologically plausible, and statistically correct compared to the IRIS (2016) EtO Assessment. The IRIS' URF of 9.1E-3 per ppb (5.0 E-3 per $\mu g/m^3$) results in a 1/100,000 excess risk concentration of 1 ppt

[1] https://[HYPERLINK "http://www.tceq.texas.gov/assets/public/implementation/tox/dsd/proposed/jun19/eo.pdf" \h]
[2] EPA/635/R-16/350Fa (December 2016)
[3] https://[HYPERLINK "http://www.epa.gov/sites/production/files/2018-10/documents/iqa" \h] petition eo- sept 2018 0.pdf
[4] Ethylene Oxide Panel Comments on EPA Proposed Amendments to "National Emission Standards for Hazardous Air Pollutants: Hydrochloric Acid Production Residual Risk and Technology Review" Docket ID No. EPA-HQ-OAR-2018-0417 (84 Fed. Reg. 1570; Feb. 4, 2019)

($0.0018\mu g/m^3$), which is inconsistent with the epidemiological and biological evidence and unreasonably conservative. The major reason for the 4000-fold difference in the URFs derived by TCEQ and IRIS is the selection of different statistical models used for low dose extrapolation.

TCEQ used mode of action (MoA) information as the primary basis for informing the low dose extrapolation, and systematically considered endogenous levels, key epidemiological data and model prediction to check and ground-truth the selection of the final model. Although IRIS (2016) also considered the MoA, toxicology and epidemiology studies for cancer classification, IRIS (2016) did not fully utilize these studies in the final selection of the extrapolation model. Instead, IRIS relied primarily on incorrect statistical analysis and flawed visual representation of the exposure-response data. TCEQ's approach to ground-truth the selection of the extrapolation model based on biological, epidemiological and statistical model prediction evidence is the critical missing step in the IRIS assessment that TCEQ completes in the proposed DSD.

ACC has five key recommendations for strengthening TCEQ's use of mode of action and epidemiological weight of evidence to ground-truth the final selection of the URFs. These recommendations will be discussed in greater detail below:

1. While TCEQ's reality check of the EPA-estimated 1 in a million to 1 in 10,000 extra risk levels is appropriate based on endogenously generated EtO relative to those contributed by exogenous EtO exposures, it can be strengthened by brief discussion of endogenously produced EtO DNA adducts.

2. TCEQ's arguments to support the selection of lymphoid cancer as the "critical cancer endpoint", while valid, would be enhanced by including a weight of evidence evaluation of the breast cancer findings from the six relevant epidemiology studies.

3. TCEQ should consider simplifying and clarifying a few sections and tables to better support TCEQ's principled approach of using MoA, biological plausibility and epidemiological weight of evidence to inform selection of the final model and the point-of-departure (PoD). The following are a couple of examples:

    - ACC[5] previously recommended use of zero-lag, but supports TCEQ's rationale for selecting the 15-year lag based on biological considerations and for consistency with the IRIS (2016) approach. Several tables can be simplified to only show the zero and 15-year lag data.
    - TCEQ should clarify that the 1/100,000 extra risk level was estimated directly from the Cox proportional hazard model. This excess risk level is at the low end of the observable range of responses consistent with EPA (2005) guidance for selecting a PoD for cancer risk assessment.

4. ACC agrees with TCEQ's emphasis on the biological mode of action and the epidemiology weight of evidence as the primary basis for selecting the type of model for low-dose extrapolation. TCEQ also provides additional statistical evidence that the final adopted TCEQ model accurately predicts the observed number of lymphoid cancer deaths in the NIOSH cohort compared to EPA's supra-linear spline model. Further clarifications and comparisons could be added to help the reader more fully appreciate these model-prediction results:

    - TCEQ should clarify in Section 3.4.1.2.2..3 that regardless of whether the maximum likelihood estimate (MLE) or the 95% upper confidence limit (UCL) model is used, the IRIS two-piece spline model over predicts the number of mortalities 95% of the time (Table 31, 95% CI).
    - In contrast, both the MLE and the UCL for TCEQ's Cox proportional hazard log-linear model accurately predict the observed mortalities.
    - Comparison of the prediction of the IRIS Cox proportional log-linear hazard model with the IRIS supra-linear two-piece spline model provides an additional "apples-to-apples" comparison based on similar IRIS assumptions for both model estimates.

5. TCEQ should clarify that contrary to EPA SAB's recommendation, IRIS used only a subset of 100 randomly chosen controls from the NIOSH data (IRIS Appendix D-4, D-29), whereas, TCEQ's model estimates are based on the full NIOSH data set.

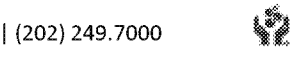
In summary, TCEQ appropriately relies on the biological MoA as the primary basis for selecting the model for low-dose extrapolation to build a strong case for why TCEQ should not adopt the EtO IRIS Assessment's inhalation of 1 in 100,000 excess risk-based air concentration of 1 ppt. TCEQ's conservative and scientifically supportable approach to an exposure response analysis should be used. This alternative approach makes use of the full data set and yields a more realistic risk-based air concentration of 4 ppb at the no significant excess risk level of 1 in 100,000.

If you have any questions or would like to discuss these comments further, please contact me at (202) 249-6714 or [redacted].

Sincerely,

William Gulledge

William P. Gulledge
Senior Director
Chemical Products & Technology Division



DETAILED COMMENTS

[SHAPE * MERGEFORMAT]

ACC agrees with the TCEQ draft DSD conclusion that the overall integrated cancer MoA assessment indicates that reliance on the EPA-hypothesized EtO supra-linear dose-response model of epidemiology data to estimate human cancer risks in the low-dose region (< 1 ppb) is not biologically plausible. This is apparent when consideration is given to doses of endogenously generated EtO exposures, and the inter-human variability of such, relative to those contributed by exogenous EtO exposures at the EPA-estimated 1 in a million to 1 in 10,000 extra risk levels. However, the formation of pro-mutagenic DNA adducts in cancer critical genes is hypothesized as the molecular initiating event[6] for the mutagenic MoA proposed by IRIS for EtO carcinogenesis. Thus, the TCEQ conclusions would be further strengthened by consideration that DNA adduct data from animal and cell-based studies are also consistent with the conclusion that EtO tumorigenicity operates by a low-dose linear and not supra-linear dose-response.

TCEQ clearly articulates toxicological MoA principles, including formation of DNA adducts, that can be used to inform selection of the most biologically plausible dose response for modeling EtO human cancer risks. TCEQ effectively emphasizes this point when stating:

> "Consideration of a direct acting DNA-reactive chemical in conjunction with normal detoxification processes and baseline levels of DNA repair enzymes that have evolved to efficiently detoxify and/or repair significant levels of endogenous EtO and associated adducts (in the endogenous range) suggests a no more than linear low-dose response component near the endogenous range where the body can no longer effectively detoxify EtO and/or repair the resulting damage."

[6]Moore MM, Schoeny RS, Becker RA, White K, Pottenger LH. 2018. Development of an adverse outcome pathway for chemically induced hepatocellular carcinoma: Case study of afb1, a human carcinogen with a mutagenic mode of action. Crit Rev Toxicol 48:312-337

This TCEQ conclusion is also consistent with the EPA IRIS statement that "it is highly plausible that the dose-response relationship over the endogenous range is sublinear".

TCEQ can further amplify this conclusion by referencing the study of Marsden et al. (2009) which provides a highly sensitive analysis of the dose-response related formation of N7-HEG DNA adducts in rats following intraperitoneal (i.p.) injections. While the kinetics of i.p. exposures may be different from inhalation exposures, it could be argued that the i.p. dosing represents a reasonable parallel to endogenously generated EtO at low doses. Furthermore, although N7-HEG is a non-mutagenic adduct, it is present at much higher levels than other potentially mutagenic DNA adducts and, in general, would be representative of a worse case for possible increase in pro-mutagenic DNA adducts.

The dose-response data from Marsden et al. (2009) provide two important MoA considerations that support at most a linear dose-response (i.e. do not support a supra-linear dose-response). First, the exquisitely sensitive methodology for assessment of DNA adducts over a 1000-fold range of EtO doses demonstrates that exogenous EtO adduct formation is conservatively represented by a low dose linear, and not supra-linear, dose response for this key MoA molecular initiating event (EPA IRIS, 2016; Moore et al, 2018; OECD, 2018). Second, and consistent with and paralleling the TCEQ analysis of the dose-response implications of endogenous EtO production evidenced by hemoglobin adduct exposure biomarkers in humans, the rat DNA data similarly show that DNA adducts resulting from low-dose exogenous EtO are a small and non-significant contributor to the overall adduct burden inclusive of endogenously-present EtO adducts. Even the inter-individual variability of endogenous DNA adducts was substantially greater than the DNA adducts contributed by low dose exogenous EtO.

Thus, these data collected from the molecular target of EtO are consistent with the conclusion of Swenberg et al. (2011)[7] that:

[7] Swenberg JA, Lu K, Moeller BC, Gao L, Upton PB, Nakamura J, Starr T. 2011. Endogenous versus exogenous DNA adducts: Their role in carcinogenesis, epidemiology, and risk assessment. Tox Sci 120: S130-S145

> "The endogenous EtO adducts outnumber the exogenous adducts by such a vast margin that the exogenous adducts are not likely to be causal for EtO-induced mutations or cancer. When looked at from the perspective of the total number of endogenous DNA adducts in a cell, it is clearly implausible."

The *in vivo* rat DNA adduct findings of Marsden et al. (2009)[8] are also consistent with the *in vitro* DNA adduct data of Tompkins et al. (2009)[9]. After a wide range of *in vitro* EtO exposures to a bacterial plasmid, increased pro-mutagenic DNA adducts and associated increased *supF* mutation frequency in human Ad293 cells were observed only after high-, but not low-concentration EtO exposures.

Taken together, these data further support and inform the overall TCEQ conclusion that the low-dose carcinogenicity of EtO conservatively operates by a low-dose linear and not supra-linear dose response.

[SHAPE * MERGEFORMAT]

For purposes of hazard assessment and consideration of breast cancer as a possible health endpoint, it is useful to examine all relevant EtO studies of female breast cancer, even those inadequate for cumulative dose-response analyses (Table 1). There is no pattern of breast cancer increase across these six studies and the overall number of observed breast cancers do not exceed expectation. TCEQ could consider including such a table in the DSD to support focus on the lymphoid cancer as the critical cancer endpoint.

[8] Marsden DA, Jones DJL, Britton RG, Ognibene T, Ubick E, Johnson GE, Farmer PB, Brown K. 2009. Dose-response relationships for N7-(2-hydroxyethyl)guanine induced by low-dose [14C]ethylene oxide: evidence for a novel mechanism of endogenous adduct formation. Cancer Res 69(7):3052–3059.

[9] Tompkins EM, McLuckie KIE, Jones, DJL, Farmer PB, Brown K. 2009. Mutagenicity of DNA adducts derived from ethylene oxide exposure in the pSP189 shuttle vector replicated in human Ad293 cells. Mut Res 678: 129-137

Table 1. Ethylene Oxide Epidemiology Studies of Female Breast Cancer

Study	Observed	Expected	Obs./Exp. (95% CI)
Coggon et al. 2004	11	13.1	0.84 (0.42, 1.51)
Steenland et al. 2004	102	103.0	0.99 (0.81, 1.20)
Steenland et al. 2003	319	367.0	0.87* (0.77, 0.97)
Mikoczy et al. 2011	41	50.9	0.81 (0.58, 1.09)
Norman et al. 1995	12	7.0	1.72 (0.93, 2.93)
Hogstedt et al. 1986	0	---	---
Summary (incident cases only)	372	424.9	0.88* (0.79, 0.97)
Summary (mortality cases only)	113	116.1	0.97 (0.80, 1.17)

The more recent study by Mikoczy et al. (2011)[10] has been incorrectly cited by IRIS (2016) as supportive of an association with breast cancer, despite an overall deficit of breast cancer, with or without consideration of a latency period. However, the two higher cumulative exposure groups had statistically significant elevated rates of breast cancer in an *internal* Poisson analysis, due to a substantial and statistically significant deficit of breast cancer in the low-dose reference group[11]. Selection of a referent group that has an unusual deficit of the disease of interest creates an artifact of an excess, as illustrated in the Mikoczy et al. (2011) study (Marsh et al. 2019[12]).

The most informative study reported overall results very close to expectation (mortality) or a significant deficit (incidence) due to case under-ascertainment (Steenland et al. 2004[13],

[10] Mikoczy Z, Tinnerberg H, Bjork J, Albin M. Cancer incidence and mortality in Swedish sterilant workers exposed to EO: updated cohort study findings 1972-2006. Int J Environ Res Public Health 2011;8(6):2009-19.
[11] Table 5 of Mikoczy et al. (2011) reports an external standardized incidence ratio (SIR) of 0.52 for breast cancer indicating a statistically significant 48% deficit in breast cancer incidence in the baseline category
[12] Marsh GM, Keeton KA, Riordan AS, Best EA, Benson SM. Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health 2019 doi: 10.1007/s00420-019-01438-z. [Epub ahead of print]
[13] Steenland K, Stayner L, Deddens J. Mortality analyses in a cohort of 18 235 EO exposed workers: follow up extended from 1987 to 1998. Occup Environ Med 2004;61(1):2-7

2003[14], respectively). The only statistically significant positive mortality trends were detected using a model with log cumulative exposure as the exposure metric and a 20-year lag (Steenland et al. 2004). With respect to breast cancer incidence modeled using a 15-year lag period in relation to log cumulative exposure, Steenland et al. (2003) noted that "The dip in the spline curve in the region of higher exposures suggested an inconsistent or non-monotonic risk with increasing exposure," which they viewed as a factor that tended "to weaken the case for a causal relationship." The inappropriateness of using a log cumulative exposure metric that forces supra-linearity has been described by Valdez-Flores et al. (2010)[15].

The breast cancer findings were weakened not only due to inconsistencies in the exposure-response, but also due to an incomplete cancer ascertainment and the subsequent potential for selection bias. Selection bias (referred to as "possible biases due to patterns of non-response" (Steenland et al. 2003)) remains a concern, however, with duration reported as a stronger risk factor than cumulative exposure in both analyses. Those who work longer and stay in the area longer are more likely to get picked up in the state tumor registries and be found for interview, therefore with the potential to impact the results of both analyses. Shorter duration workers with lower cumulative exposures are more likely to leave the area and not be captured in the overall analyses and less likely to be interviewed. Their diagnoses may get missed, creating a possible biased positive exposure-response. Steenland et al. (2003) recognized this limitation and admitted he was unable to fully address it.

The above arguments support TCEQ's decision to exclude breast cancer as "a critical cancer endpoint" in the estimation of a URF. Furthermore, these arguments also demonstrate that EPA's reliance on this study as the primary justification for a supra-linear slope is not

[14] Steenland K, Whelan E, Deddens J, Stayner L, Ward E. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control 2003;14(6):531-9.
[15] Valdez-Flores C, Sielken RL, Jr., Teta MJ. Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to EO. Regul Toxicol Pharmacol 2010;56(3):312-20.

scientifically sound. The following are a few additional specific comments regarding breast cancer incidence:

2.1 **p. 60-** last paragraph regarding Table 10. TCEQ states that "NIOSH breast cancer incidence data were not publicly available for independent analysis. Therefore, Table 10 results will not be utilized." Perhaps these two sentences can be switched in order to improve clarity:

> Regarding Table 10, the log-linear model did not fit the breast cancer mortality data statistically better than the null model (zero slope). However, it does fit the breast cancer incidence data better than the null model . . . Therefore, the TCEQ will not utilize Table 10 results, but rather consider log-linear (standard Cox regression) 15-year exposure-lagged model results for breast cancer incidence (subcohort with interviews) from USEPA (2016). Unfortunately, the NIOSH breast cancer incidence data were not publicly available for independent analysis. Therefore, the TCEQ will use Table 11 adapted from Table 4-12 of USEPA.

2.2 **p. 64-** first sentence in italics explains the rationale for ignoring breast cancer incidence excess risk. This section should incorporate consideration of the weight of evidence for breast cancer incidence described under Key Comment #2 above. The epidemiology data does not support a potency for breast cancer that is stronger than for lymphoid cancer.

2.3 **p. 84 and 90-** the statement is made in reference to Swaen et al. (2009)[16] and Mikoczy et al. (2011)[17] that "Healthy Worker Effect (HWE)" likely influenced results". HWE is a well-known form of bias in occupational cohort studies in which increased risks may be missed when comparisons are made to an external, general population, considered to be less healthy than the worker population. However, the epidemiologic literature has shown that HWE is predominately related to shorter follow up and non-cancer causes (Monson 1986[18]; Fox and Collier 1976[19]). Swaen (2009) had a very long follow up (36.5 yr. average) and deficits in major non-cancer

[16] Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM. Mortality study update of EO workers in chemical manufacturing: a 15 year update. J Occup Environ Med 2009;51(6):714-23.
[17] Mikoczy Z, Tinnerberg H, Bjork J, Albin M. Cancer incidence and mortality in Swedish sterilant workers exposed to EO: updated cohort study findings 1972-2006. Int J Environ Res Public Health 2011;8(6):2009-19.
[18] Monson RR. Observations on the healthy worker effect. J Occup Med. 1986 Jun;28(6):425-33. https://[
HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/3723215" \h]
[19] Fox AJ, Collier PF. Low mortality rates in industrial cohort studies due to selection for work and survival in the industry. Br J Prev Soc Med 1976; 30:225-30

causes only among those hired after 1956. There is no indication that cancer increases have been missed due to HWE. Similarly, for Mikoczy et al. (2011), mortality was no longer decreased with a 15 yr. "induction latency" period. A study to test HWE in Sweden as it relates to breast cancer has been published showing no HWE (Gridley et al. 1999[20]). To avoid misleading the reader, we recommend deleting these statements in the report or specifying that they relate to non-cancer causes.

[SHAPE * MERGEFORMAT]

3.1 Table 6 (p. 56) includes some cancer endpoints that are not relevant based on the epidemiological weight of evidence. This table should only include lymphohematopoietic and breast cancers, which are the only cancers that IRIS (2016, p. 3-13) associated with EtO exposures.

3.2 Table 7-10, 12-14 (pp. 57-62) can be simplified to just show the zero and 15-year lag. TCEQ should indicate in the text and footnote of these tables that a large number of lag periods were tested and none were statistically different from zero lag. ACC previously recommended use of zero-lag, but supports TCEQ's rationale for selecting the 15-year lag based on biological considerations and for consistency with IRIS (2016) approach. However, it should be noted that in some cases the 95% UCL URFs for zero lag were slightly higher (more conservative) than for the 15-year lag.

3.3 Section 3.4.1.5.2 Risk-Based Concentrations and URFs and Tables 12-14 should add explanations that the 1/100,000 extra risk level was estimated directly from the Cox

[20] Gridley G, Nyren O, Dosemeci M, Moradi T, Adami HO, Carroll L, Zahm SH. Is there a healthy worker effect for cancer incidence among water in Sweden? Amer J Indust Med 36:193-199

proportional hazard model, and that this is consistent with EPA (2005[21]) cancer guidelines on selection of the PoD at the low end of the observable range of responses. For example, with rodent models, a 10% (1 in 10) PoD is typically used as a 10% extra risk and is near the limit of detection for a typical assay. For epidemiologic data, a lower PoD can be used. When the standard Cox proportional hazard (log-linear) model is used for the NIOSH males-only 15-year lag data, all of the lymphoid mortalities with non-zero exposure occurred **below** the 1 in 100 PoD (Table 2). Therefore, 1 in 100 is not an appropriate PoD for "extrapolation" in the conventional sense.

Table 2. Number of male lymphoid cases out of approximately 18,000 workers with concentrations below the EC (1/100) and EC (1/100,000)

	Male Lymphoid EC 1/100		Male Lymphoid EC 1/100,000[2]	
	0-Lag	15-Lag	0-Lag	15-Lag
EC (1/100,000) Env. Conc (ppm)	3.52	5.80	5.83E-03	9.67E-03
Equivalent[1] Occupational Exposure 70 years (ppm-days)	326,105.9[2]	354,399.0[2]	453.4[2]	590.87[2]
Total Number of Deaths	27	27	27	27
Number with zero exposure	0	6	0	6
Number With Non-Zero Exposure below EC	27	21	1	1

[21] EPA (2005) Guidelines for Carcinogen Risk Assessment. https://[HYPERLINK "http://www.epa.gov/sites/production/files/2013-" \h] 09/documents/cancer_guidelines_final_3-25-

Percentage of Deaths below EC	100%	100%	3.70%	25.93%

[1]Equivalent Occupational Exposure 70 years (ppm-days) = EC×(365/240)×(20/10)×365.25×(70-lag)

[2]The maximum occupational exposure concentration for lymphoid deaths was less than 326,106 ppm-days for the unlagged and 137,243 ppm-days for the 15-year lag exposure.

A typical POD extrapolates from the edge of the observed range through the unobserved range of the data. Thus, for the NIOSH male only data, it is appropriate to use the model to extrapolate to 1 in 100,000, which is below the 50th percentile of exposure where there is only one lymphoid mortality for subjects with non-zero exposure.

IRIS (2016) used a 1% (1 in 100) extra risk for the PoD but did not provide evidence that this level would establish a PoD near the edge of the observed data range. ACC does not have the NIOSH data to determine the validity of the 1% for the supra-linear spline model.

3.4 The Cox proportional hazard model selected by TCEQ has the form exp(β z) and is usually described as a sublinear model. However, this model becomes linear at extra risk levels of 1/100,000 and lower as concentration "z" approaches zero. Selection of this model is appropriate based on mode of action considerations which indicate that the exposure response is no more than linear.

[SHAPE * MERGEFORMAT]

4.1 **P. 41-46, Section 3.4.1.2.2.3**: TCEQ used the final selected 95% upper confidence limit (UCL) model to predict lymphoid mortalities. TCEQ may want to further clarify that regardless of whether the maximum likelihood estimate (MLE) or the 95% upper confidence limit (UCL) model is used, the IRIS two-piece spline model over predicts the number of mortalities 95% of the time (Table 31, 95% CI).

4.2 In contrast, the MLE and UCL models for TCEQ's Cox proportional log-linear model accurately predicts the number of mortalities. The section on model prediction analysis could also clarify that this comparison is based on the model fit prior to any additional adjustments based on age or other factors.

4.3 **Figures 8 to 12:** TCEQ might consider including IRIS's Cox proportional log-linear model in Figures 8 to 12 for comparison with IRIS's supra-linear two-piece spline slope. Comparison of the prediction of the IRIS Cox proportional log-linear hazard model with the IRIS supra-linear two-piece spline model provides an additional comparison based on similar IRIS approach (i.e. using a random subset of the data). .

[SHAPE * MERGEFORMAT]

5.1 EPA SAB recommended that IRIS utilize the full NIOSH data set to estimate the cancer slope coefficients that would in turn be used to extrapolate risk instead of a small subset used by IRIS (IRIS Appendix H-10).

5.2 TCEQ's model estimates are based on the full NIOSH data set. However, the IRIS (2016) model use the subset of 100 controls. There is no strong biologic or statistical justification for selecting a subset of the data to estimate dose response curves. Thus, TCEQ's analysis is a more robust and complete analysis based on all the available data.

ADDITIONAL COMMENTS

- **3.6 p. 14 and p.27** authorship should be corrected in the section in italics regarding update of the UCC cohort. Dr. Valdez-Flores is not a co-author of the Bender et al. 2019 paper (submitted), but is an author of a risk assessment paper based, in part, on the Bender et al. 2019 paper.
- **3.9 p.25, para.2:** This text effectively describes how the implausibly high cancer risk associated with low dose EtO exposures as estimated by EPA also infers an implausibly high cancer risk associated with exogenous long term exposure to ambient levels of ethylene (due to its metabolism to EtO). However, the analysis should be expanded to clarify that, unlike EtO, the current risk assessments for ethylene are based on robust negative chronic rodent inhalation bioassays and genotoxicity assessments, and thus should not be targeted for cancer risk reevaluation based on extrapolation from the EPA EtO cancer risk assessment.
- **3.10.p. 31 Table 4** A footnote should be added next to Valdez-Flores et al. 2010 that only the first and fourth column are based on data from Valdez Flores et al. 2010.
- **p.31 Table 4** The breast cancer row incorrectly indicates the highest 5th quantile is elevated risk, but we believe this is incorrect because there was no statistical increase. Instead it should indicate Not Applicable.
- **p. 32 Table 5** Similar to Table 4, a footnote should be added to clarify that only columns 1 and 4 are from Steenland et al. (2004, 2003) and that other values were estimated by TCEQ.
- **p. 57-60** This series of tables was difficult to follow. We recommend separating the p-value vs. null and p-value vs. zero lag into separate columns by themselves.